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EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/679,123	KLINKSIEK ET AL.	
	Examiner	Art Unit	
	SNIGDHA MAEWALL	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-40,42,44 and 45* is/are pending in the application.

5a) Of the above claim(s) *1-15 and 37-39* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *16-36,40,42,44 and 45* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of Applicants arguments/remarks, amended claims and **RCE** filed on 08/05/11 are acknowledged.

Claims 1-15, 37-39 remain withdrawn. Claims 41 and 43 remain cancelled.

Claims have been amended to recite crystalline structure.

Claims **16-36, 40, 42 and 44-45** are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims **16-36, 40, 42 and 44-45** are rejected under 35 U.S.C. 103(a) as being unpatentable over Irvin et al. (USP 7,276,184) in view of Westesen et al. (US Patent No. 5,885,486) and further in view of JORDAN et al. (US PG pub. 2002/0103285 A1).

Irvin et al. teaches preparation of nanoscale particulate material comprising functional materials which are solids at ambient temperature in conjunction with a surfactant/dispersant material within a carrier fluid carbon dioxide which is a compressed gas or supercritical fluid phase, depressurization of this mixture results in evaporation of carrier fluid which is carbon dioxide in this case and resulting in formation of nanoscale particles, see column 5, lines 10-25. The temperature used is from range of zero to hundred degrees Celsius and preferably from 10 to 60 degrees Celsius, see column 5, lines 47-50. The reference teaches that the nano materials have dimensions from 0.5 nm to 10 nm and can be solid or fluid –like properties, the nano fluid can be facilitated by the use of high molecular weight surfactant to functional material, see column 9, lines 15-25. Various surfactant described are ethylene and propylene oxides, alcohols, amides and esters, see column 6, lines 45-55.

The reference does not teach freeze drying or spray drying of dispersion and the reference also does not teach coating material.

Westesen et al. discloses an invention relating to the area of administration forms and delivery systems for drugs, vaccines and other bioactive agents. The reference also describes the process of preparing micron and submicron particles of bioactive agents. The process as depicted describes that a solid lipid or bioactive agent or a mixture of solid lipids is melted; stabilizers are added either to the lipid or bioactive agent or to the aqueous phase only depending on their physicochemical characteristics. Stabilizers may also be added or exchanged after homogenization. (Abstract).

Drugs or bioactive agents can be melted together with lipid. Solid lipid particles such as fatty acids and their esters are disclosed on column 9, lines 23-25. Various drugs have been disclosed in column 10, lines 30-60. The bioactive agents can be dissolved, solubilized and dispersed in the matrix, see column 10, lines 61-64. The reference teaches that drugs or bioactive substances may be melted or may be dissolved, solubilized or dispersed in the lipid melt, see column 11, step (4). The melted lipid compounds are emulsified in the dispersion medium, see step (5) on column 11. **Sucrose and glucose** are taught as **stabilizers in** column 15, lines 35-38. **Propylene glycol** is taught in column 15, lines 40-45. Glycerol is taught in example 26.

The aqueous phase is heated to the temperature of the melt before mixing and may contain for example, stabilizers, isotonicity agents, buffering substances, and /or preservatives. The molten compounds are **emulsified** in an aqueous phase by **high pressure homogenization (abstract**, column 11 and steps 1-8). Drugs or bioactive agents particularly suitable are listed in column 10, lines 30-60). Ibuprofen and vitamins are also enlisted on the same column. Further in step 8 in column 11, lines 50-55, it is disclosed that the dispersion medium can be reduced by standard techniques such as **freeze drying and the lyophilized powder** can also be processed into other pharmaceutical formulations such as tablets etc. Regarding the end product being emulsion, the prior art teaches that the melted lipid compounds are emulsified in dispersion medium (see step (5) in column 11 (instant specification , on page 20, teaches in lines 27-28 that the heating step is for very short time such that the emulsion state is present for short time).

The bioactive drugs can be in dissolved or **crystalline or amorphous** or a mixture of these crystallographic states. Role of surfactant is described in example 19 on column 24. Various isotonicity agents such as glycerol or xylitol and sucrose, glucose are disclosed on column 10, lines 10-15. The suspensions and lyophilizates can be used for peroral, buccal, pulmonary etc. depending on the particle size (see column 14, lines 40-45). The reference further teaches the importance of smaller particle size during drug delivery process (see column 2, lines 10-25). The reference teaches that the drug carrier systems in the micrometer size range are represented as microspheres which are encapsulated (column 3, lines 30-35). The mean particle size lies in nanometer range and is prepared by emulsion polymerization or by solvent evaporation, see column 3, lines 35-37. The submicron size is of less than 50 nm is shown in column 6, lines 50-53.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the drying process of freeze drying as taught by Westesen et al. in to the teachings of Irvin et al. because both the references are directed towards teaching preparation of nanoparticulate formulation for drug delivery. One of ordinary would have been motivated to utilize the known freeze drying process of Westesen et al. into the known process of forming nanoscale particles as taught by Irvin et al. Regarding various temperatures and pressures recited in claims 17-25 and claims 32-33, it is the position of the Examiner that one of ordinary skill would have recognized varying temperatures and pressure to optimum degrees since prior art by Irvin teaches utilization of temperature and pressure during nano particle formation of substance. One

of ordinary would have envisaged utilizing optimum temperature and pressure limitations in order to obtain nano particulate pulverized particles for drug delivery absent evidence of any criticality shown by applicants. Addition of various additives would have been obvious since the references teach addition of sugar, glycerin and stabilizers etc. It is further to be noted that addition of such ingredients are optional as claimed.

The combined teachings of references discussed above do not teach polyvinyl alcohol or hydrolyzed polyvinyl acetates as coating material as claimed and utilization of spray drying technique.

JORDAN et al. disclose film coatings and film coating compositions based on polyvinyl alcohol, see title. The reference discloses dry film coating composition for use in coating pharmaceutical tablets, nutritional supplements etc. comprising polyvinyl alcohol, abstract. The polyvinyl alcohol comprises partially hydrolyzed polyvinyl acetate which has percentage of hydrolysis greater than about 86.5% mol. % and preferably from 86.5 to 89.0% mol, see page 2, [0020]. The coating on the tablets possess an excellent long lasting shining gloss, minimal tackiness, good film adhesion and good tensile strength, see [0033] and examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the partially hydrolyzed polyvinyl acetates, that is polyvinyl alcohol in the teachings of the references discussed above for the excellent shining, minimal tackiness and good film adhesion motivated by the teachings of JORDAN et al. Utilization of known coating material would have produced predictable

results. Utilization of known spray drying technique would have been obvious to one of ordinary skill in the art at the time of instant invention because JORDAN et al. teaches particle formulation by spray drying. The claimed invention thus would have been obvious within the meaning of 35 USC 103. Regarding the claimed property of avoiding recrystallization, it is the position of the examiner since prior art makes obvious use of polyvinylalcohol coatings, one would expect the property to be associated with it absent evidence to contrary.

4. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Irvin et al. (USP 7,276,184) in view of Westesen et al. (US Patent No. 5,885,486) , (JORDAN et al. (US PG pub. 2002/0103285 A1) as discussed above and further in view of Rochling et al. (USP 6,602,823).

The references taught above generically teach additives in the preparation. The references do not teach each and every additive claimed in claim 42. Rochling teaches various specific additives that are known to be utilized in the formulations. Rochling teaches dispersants such as gelatin, starch, polyvinyl alcohol, polyvinylpyrrolidone and preservatives in column 6, lines 50-65. Fillers such as carbonates and silicates silica gels in column 7, lines 1-10.

It would have been obvious to one of ordinary skill in the art to substitute specific additives in formulation of the Irvin and Westesen motivated by the teachings of Rochling et al. because these ingredients are known to be added as additional

components in pharmaceutical art. It is further to be noted that addition of such ingredients are optional as claimed.

Applicant argues that Rochling does not overcome Irvin, Westesen and JORDON's differences from the claimed invention. These arguments are not persuasive because Rochling has been cited for various dispersants used in pharmaceutical art.

CITED AS OF INTEREST

USP 2,702,264 has been cited as of interest to show that partially hydrolyzed polyvinylacetates were used as coating material in enteric coated tablets.

Response to Arguments

5. Applicant's arguments filed 07/28/11 have been fully considered but they are not persuasive.

Applicant argues that It is totally surprising that the active ingredient (A), which was initially in crystalline form, remains in amorphous form and does not recrystallize (paragraph [0032]). As a result of this, the bioavailability of the active ingredient remains very high (paragraph [0033]). Applicant then points to various sections in Irvin and points to Westesen where product is recrystallized and argues that Irvin and Westesen teach crystalline drug on pages 14-16 of arguments. Applicant adds that those skilled in the art understand that an amorphous formulated drug is resorbed by the human body much faster than the same drug if in a crystalline state. Thus, Applicants' invention represents a tremendous differences between Applicants' invention and anything that

could be learned from the of Irvin/Westesen/Jordan combination of references. The Examiner relies on Rochling for specific additives. None of the additives taught by Rochling could possibly overcome the differences discussed above.

Applicants' invention discloses particle of an active ingredient, which is normally in crystalline form but which has been transformed into amorphous form, before it could recrystallize and thereby prevent it from recrystallizing. Nothing in Jordan suggests that the tablets e.g. of Jordan's Example 1 were a type that was in amorphous form, but which would recrystallize to a crystalline form and that the coating was applied before recrystallization took place and prevented such recrystallization. Moreover, as discussed above, the Irvin/Westesen combination of references pertain to an active ingredient in crystalline (not amorphous) form. If one were to coat the Irvin/Westesen particles with Jordan's dry film coating, one would end-up with a particle in crystalline form, coated The differences between Applicants' invention and anything that could be learned from the of Irvin/Westesen/Jordan combination of references are discussed above. The Examiner relies on Rochling for specific additives. None of the additives taught by Rochling could possibly overcome the differences discussed above.

These arguments are not persuasive. In response to applicants arguments that nothing in Jordan suggests that the tablets e.g. of Jordan's Example 1 were a type that was in amorphous form, but which would recrystallize to a crystalline form and that the coating was applied before recrystallization took place and prevented such recrystallization, It is pointed out that Jordan was quoted for teachings of coating actives

with polyvinyl acetates. The advantage that applicant has discovered due to such coating would be obvious because property cannot be separated from the chemistry of compound. In this regard, the examiner points to instant specification on page 5, second paragraph which states that "It is extremely surprising that the pulverulent active substance formulations of the invention are substantially more stable than the existing preparations constitutionally closest to them, which are obtainable by melt dispersing, but in which the individual particles **are not encapsulated**". Therefore in light of this it is evident that Jordan's teachings of coating with polyvinyl acetates for use in coating pharmaceutical tablets, nutritional supplements etc. comprising polyvinyl alcohol, wherein the polyvinyl alcohol comprises partially hydrolyzed polyvinyl acetate which has percentage of hydrolysis greater than about 86.5% mol. % and preferably from 86.5 to 89.0% mol, provides an excellent long lasting shining gloss, minimal tackiness, good film adhesion and good tensile strength, (see page 2, [0020] and [0033] and examples) will also provide the similar film adhesion and tensile strength and thus will provide the argued/claimed stability of active ingredient in amorphous form which does not recrystallize or provides better bioavailability. It is pointed out that reference does teach the process of coating with polyvinyl alcohol, therefore, property of being capable of avoiding recrystallization of the active substance will be obvious because property cannot be separated from the chemistry of compound. Patent office is not equipped with laboratory to provide the experimentation, burden is on applicant to provide evidence that prior art's polyvinyl acetate will not provide the same effect. Patent office is not equipped with laboratory to provide experimentation to prove the property. Office has

provided rationale for obviousness and burden is on applicant to prove otherwise. Irvin teaches solid active material in nanoscale and Westesen teaches active agents can be in amorphous form and Jordan provides motivation to add coating to pharmaceuticals. Besides the argued unexpected results are due to specific active ingredient, specific emulsifier and specific coating component in specific particle size and in specific amounts as shown in examples 1-2. The results argued therefore do not commensurate with the entire scope of instant claims which recites various dispersants. Rochling was added for optional additives, the rejections will be maintained.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S. Kishore/

Primary Examiner, Art Unit 1612